REMARKS

Status of the Claims

Claims 1 and 5 are pending in the application. Claims 1 and 5 are rejected. Claim 1 is amended. No new matter is added herein.

Claim Amendments

Claim 1 is amended to overcome the 35 U.S.C. §112, first paragraph rejection. Amended claim 1 recites a method of treating uterine serous papillary carcinoma that over-express HER-2/neu. Such a method consists of the step of administering to an individual with the carcinoma a therapeutically effective dose of a humanized murine anti-HER2/neu monoclonal antibody 4D5 where the antibody is an IgG1k that contains human framework regions with the complementary-determining regions of the murine monoclonal antibody 4D5 that binds to the extracellular domain of HER-2/neu. The inclusion of the structure of the humanized murine anti-HER2/neu monoclonal antibody 4D5 in the amended claim is supported by the teachings of the instant specification (Example 3).

The 35 U.S.C. §103 Rejection

Claims 1 and 5 remain rejected under 35 U.S.C. §103 for the reasons previously set forth in the Paper mailed February 7, 2005, Section 3, pages 2-9. Applicant respectfully traverses this rejection.

The Examiner maintains that **Pegram** *et al* teach the effectiveness of the antibody alone for *in vivo* treatment. Further, the Examiner states that **Bookman** *et al* teach that 39% of the patients met the criteria for stable disease on treatment with HERCEPTIN® alone. Based on this, the Examiner contends that despite the suggested combination of HERCEPTIN® with cisplatin, it was clear that one of ordinary skill in the art would have reasonable expectation of success in treating any cancer that overexpresses HER-2/neu with HERCEPTIN® alone (page 5 of previous Office Action).

The Examiner finds Applicant's argument regarding the combination of the prior art references not teaching or suggesting all of the elements of Applicant's amended claim unpersuasive. The Examiner's reason for this is the purported misrepresentation of the teachings of **Pegram** *et al* by the Applicant. The Examiner maintains that **Pegram** *et al* do not teach that the treatment with HERCEPTIN® alone was not effective but that the response rates with the combination therapy was higher than that of anti-Her-2/neu monoclonal antibody alone. Further, the Examiner states that the Applicant's argument regarding teaching in **Bookman** *et al* of combining HERCEPTIN® with platinum based therapy due to low freqency of HER-2/neu expression and very low reponse rates to single agent HERCEPTIN® unpersuasive. The reason for this as stated by the Examiner is the teaching in **Berchuk** *et al.*, **Saffari** *et al* and **Wang** *et al* of high frequency of HER-2/neu overexpression in uterine papillary carcinomas. Hence, based on this reasoning, the Examiner argues that one would have reasonable

expectation of success in treating at least a subset of patients having papillary carcinomas with HERCEPTIN® alone. Applicant respectfully disagrees.

As the Examiner is aware, **Bookman** *et al* is not a prior art reference against the instant invention since it has a publication date (January 2003) that falls after the filing date (September 2001) of the instant invention. Applicant respectfully disagrees with the Examiner's interpretation of the teachings of **Pegram** *et al*. **Pegram** *et al* teach that the overall response rate with cisplatin alone, recombinant humanized anti-HER-2/neu monoclonal antibody (rhuMAb HER2) alone and the combination of cisplatin and rhuMAb HER2 to patients with HER-2/neu over-expressing breast cancers was 7%, 12% and 24%, respectively (page 2667, col I, line 3-page 2668, line 4).

Furthermore, **Pegram** *et al* teach that the observed response to rhuMAb HER2 (12%) was due to a combination of a decrease in cell proliferation and antibody-dependent cellular cytotoxicity induced by rhuMAb HER2. Additionally, **Pegram** *et al* teach that the observed response (24%) to combination therapy was due to the additive effects from each agent alone (page 2668, col. II, lines 5-50). **Pegram** *et al* further teach that based on the response rates, the combination therapy may be a viable therapeutic approach for treating Her-2/neu over-expressing breast cancer (page 2669, col. II, last paragraph). Thus, in general, **Pegram** *et al* teach that the combination therapy rather than rhuMAb HER2 alone is a better therapeutic approach to treat Her-2/neu-over-expressing cancers. Given this teaching, one of ordinary skill in the art would use a combination therapy rather than rhuMAB HER-2 alone to treat such cancers. Hence, Applicant contends that

the combination of prior art references (**Berchuk** *et al.*, **Saffari** *et al.*, **Wang** *et al.* and **Pegram** *et al*) neither suggest all elements of the amended claim 1 nor does it provide one of ordinary skill in the art with the incentive to use rhuMAb HER-2 alone to treat Her-2/neu over-expressing uterine serous papillary carcinoma with reasonable expectation of success.

Additionally, **Bookman** *et al* (published after **Pegram** *et al*) demonstrated a response rate of 7.3% (3 out of 41 patients) to rhuMAB HER-2 alone that was lower than the 12% response rate observed by **Pegram** *et al.* Furthermore, the teaching in the art regarding the use of rhuMAb HER-2 at the time the instant invention was filed pointed to the use of rhuMAb HER-2 in combination with chemotherapeutic agents or other cytotoxic drugs (see *Semin Oncol* 2001, Aug, 4 Suppl 15: 71-6; *Cancer Biother Radiopharm* 1999, Feb, 14(1): 5-10; *Semin Oncol* 2000 Apr, 27(2 Suppl 3): 19-23, *Clin Breast Cancer* 2001, Oct 2, Suppl 1:S15-9; *Anticancer Drugs*, 2001, Dec 12, Suppl 4: S19-25; *Anticancer Drugs*, 2001, Dec 12, Suppl 4: S3-10; *Oncology*, 2001, 61(suppl 2): 31-6). Hence, Applicant further contends that if one of ordinary skill in the art were motivated to treat Her-2/neu over-expressing uterine serous papillary carcinoma with rhuMAb HER2 as claimed in the instant invention with reasonable expectation of success, one would be merely "trying" to arrive at the claimed invention due to the variability in the response rates to rhuMAB HER-2 alone. It has long been established that trying is not the standard for obviousness under 35 U.S.C §103. Accordingly, based on these remarks, Applicant respectfully requests the withdrawal of rejection of claims 1 and 5 under 35 U.S.C. §103.

The 35 U.S.C. §112, First paragraph Rejection

Claims 1 and 5 remain rejected under 35 U.S.C. §112 for reasons previously set forth in the Paper mailed February 7, 2005, Section 4, page 9. Applicant respectfully traverses this rejection.

Although the Applicant had shown support in the instant specification in addition to the knowledge common to those of ordinary skill in the art regarding HERCEPTIN® to be a humanized murine monoclonal antibody 4D5, the Examiner states that the Applicant is arguing limitations not recited in the claims as currently constituted. The Examiner further states that the claims as currently constituted are not drawn to HERCEPTIN® but rather to any humanized murine anti-HER2/neu 4D5 monoclonal antibody with alterations in the framework or variable regions that are different from those of HERCEPTIN® for which the specification provides no support. Hence, the Examiner has maintained the previous 35 U.S.C §112 rejection.

Applicant has amended claim 1 which now recites the structure of humanized murine anti-HER2/neu antibody with regards to the framework and variable regions as discussed supra. This amendment is supported by the teachings of the instant specification. Accordingly based on this amendment and remark, Applicant respectfully requests withdrawal of rejection of claims 1 and 5 under 35 U.S.C. §112, first paragraph.

This is intended to be a complete response to the Final Office Action mailed May 17, 2005. Applicants submit that the pending claims are in condition

for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicant also encloses a petition to extend the time for filing this response for one (1) month to and including December 24, 2005. Please charge the $60 extension fee to the credit card identified on the enclosed PTO-2038. In the absence of this form, please debit the fees due from Deposit Account No. 07-1185 on which Applicant's counsel is allowed to draw.

Respectfully submitted,

Date: 12/2/05

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1: Semin Oncol. 2001 Aug;28(4 Suppl 15):71-6.

Related Articles Links

Docetaxel, estramustine, plus trastuzumab in patients with metastatic androgen-independent prostate cancer.

PubMed Services

Small EJ, Bok R, Reese DM, Sudilovsky D, Frohlich M.

Urologic Oncology Program, University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA 94143-1711, USA.

Related Resources

The incidence of human epidermal growth factor receptor 2 (HER2) protein overexpression and its prognostic value are not well characterized in patients with prostate cancer. A phase I study was designed to evaluate docetaxel/estramustine plus trastuzumab, a humanized monoclonal antibody that binds to the HER2 receptor, in patients with metastatic androgen-independent prostate cancer (AIPC). HER2 positivity was not required because safety was the primary endpoint. Patients received oral estramustine 280 mg three times daily (days 1 to 5); docetaxel, 70 mg/m(2) intravenously (day 2); and trastuzumab, 2 mg/kg intravenously (days 2, 9, and 19), every 21 days until the disease progressed or toxicity became unacceptable. This regimen was well tolerated among the first 13 treated patients. Grade 4 neutropenia was seen in 10% of administered cycles. There were two episodes of febrile neutropenia and two thrombembolic events. Of the 13 patients evaluable for prostate-specific antigen (PSA) response, nine (69%) experienced a decrease in PSA level of >50%. Two (33%) of six patients with measurable disease had objective responses, and one complete response was seen on bone scan. Docetaxel/estramustine/trastuzumab appears to be a safe combination when used in the treatment of metastatic AIPC. The response data are too preliminary for speculation about the relative benefits of this 3-drug regimen compared with the combination of only docetaxel and estramustine in this clinical setting.

Publication Types:

1: Cancer Biother Radiopharm. 1999 Feb;14(1):5-10.

Perceptions of Herceptin: a monoclonal antibody for the treatment of breast cancer.

Dillman RO.

Hoag Cancer Center, Newport Beach, California 92658, USA.
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In September 1998 Trastuzumab (Herceptin) became the second monoclonal antibody approved for the treatment of a malignant condition, and the first antibody approved for the treatment of a solid tumor. It is a mouse-human chimeric antibody that produces anti-tumor effects by blocking the HER2-neu receptor, and can also interact with human immune cells to effect antibody dependent cell-mediated cytotoxicity. Pivotal trials in breast cancer showed that it has activity as a single agent in a subset of patients whose tumors greatly over-express HER2, but results were even more impressive when it was used in combination with chemotherapy. It should also prove to be useful in the treatment of subsets of patients with other adenocarcinomas whose tumors over-express HER2.

Publication Types:

- Review
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PMID: 10850281 [PubMed - indexed for MEDLINE]

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1: Semin Oncol. 2000 Apr;27(2 Suppl 3):19-23. Related Articles, Links

Docetaxel (Taxotere) in HER-2-positive patients and in combination with trastuzumab (Herceptin).

Burris HA 3rd.

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In addition to being an important indicator of poor prognosis, human epidermal growth factor receptor-2 (HER-2) status may help identify those patients in whom chemotherapy is the most appropriate choice of therapy. In several studies, including a trial of sequential neoadjuvant therapy in which certain patients received docetaxel (Taxotere; Rhone-Poulenc Rorer, Antony, France) following four courses of cyclophophamide 1000 mg/m2, doxorubicin 50 mg/m2, vincristine 1.5 mg/m2 on day one, and prednisone 40 mg by mouth for 5 days, HER-2 positivity predicted response (including pathologic response) to chemotherapy. In vitro and in vivo, docetaxel has demonstrated true synergy with the recombinant human anti-HER-2 monoclonal antibody trastuzumab (Herceptin; Genentech, San Francisco, CA). In a phase III study comparing trastuzumab alone with trastuzumab plus chemotherapy (either paclitaxel or doxorubicin plus cyclophosphamide), combining the antibody with cytotoxic drugs increased response duration, time to progression, and survival in first-line metastatic breast cancer patients. Preliminary clinical data suggest that the combination of trastuzumab with docetaxel is active and well tolerated, and pilot studies of adjuvant therapy using trastuzumab and docetaxel combinations are under way in high-risk patients.

Publication Types:

- Review
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1: Clin Breast Cancer. 2001 Oct;2 Suppl 1:S15-9. Related Articles, Links

Combining the anti-HER2 antibody trastuzumab with taxanes in breast cancer: results and trial considerations.

Pegram MD, O'Callaghan C.

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Overexpression of the p185/HER2 protein is seen in 20%-25% of primary breast cancers and is associated with poor prognosis. Recent phase II and III clinical trials demonstrate that trastuzumab is active against breast tumors, both as a single agent and in combination with chemotherapy. In patients with HER2-overexpressing metastatic breast cancer, use of trastuzumab in combination with chemotherapy is associated with a 20% reduction in relative risk of death and an increase in median survival from 20.3 to 25.1 months compared to chemotherapy alone. Side effects include fever and chills and an unexpected increase in doxorubicin/trastuzumab-associated cardiomyopathy. Clinical development is now focused on trastuzumab in combination with chemotherapy regimens that do not contain an anthracycline. Trastuzumab in combination with docetaxel is synergistic in vitro. Data from ongoing clinical trials are consistent with this finding. Preliminary data from 3 phase II studies suggest a 44%-63% response rate when the combination is used first or second line in HER2-overexpressing metastatic breast cancer. The combination of docetaxel with trastuzumab is well tolerated and has not been associated with significant cardiotoxicity. Given in vitro evidence that platinum salts act synergistically with trastuzumab and docetaxel, and phase II data suggesting clinical efficacy and good tolerability, the combination of platinum salt plus trastuzumab and docetaxel is now being assessed in adjuvant trials

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1: Anticancer Drugs. 2001 Dec;12 Suppl 4:S19-25. Related Articles, Links

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Trials of new combinations of Herceptin in metastatic breast cancer.

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Herceptin extends survival in human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer patients when administered with paclitaxel or anthracycline/cyclophosphamide (AC), and the combination with 3-weekly paclitaxel is the current standard first-line therapy. However, other combinations may be equally effective. This review provides information on recent and ongoing trials of new Herceptin combinations. Preliminary results indicate that Herceptin plus epirubicin/cyclophosphamide may be effective without the cardiotoxicity of the AC combination. Weekly paclitaxel plus Herceptin has produced responses in 83% of HER2-positive patients treated. Co-administering Herceptin with other cytotoxic agents has also been investigated, with combination partners being chosen based on in vitro synergy with Herceptin, known efficacy as monotherapy and convenience of weekly administration (e.g. docetaxel, vinorelbine). High response rates have been observed in these clinical trials, e.g. up to 80% in combination with vinorelbine. Furthermore, Herceptin in combination with weekly paclitaxel, docetaxel or vinorelbine was well tolerated: there was no significant cardiotoxicity or unexpected toxicity and the combination showed an adverse event profile similar to that seen with monotherapy with the cytotoxic agent. Thus, Herceptin produces additional clinical benefit when added to all the cytotoxic agents with which it has been examined, further demonstrating its potential for use in HER2-positive breast cancer patients.

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1: Anticancer Drugs. 2001 Dec;12 Suppl 4:S3-10. Related Articles, Links

Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies.

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Amplification of the human epidermal growth factor receptor-2 (HER2) gene and overexpression of the encoded protein are seen in 20-30% of breast cancers, and are associated with aggressive disease and relatively poor prognosis. Thus, HER2 represents an appropriate target for anticancer treatment and the humanized anti-HER2 monoclonal antibody Herceptin has been developed for this purpose. The efficacy of Herceptin has been confirmed in two pivotal trials-a monotherapy study in 222 women with HER2-positive metastatic breast cancer who had already received one or two chemotherapy regimens for metastatic disease and a study comparing Herceptin plus chemotherapy with chemotherapy alone in 469 patients previously untreated for metastatic disease. Herceptin monotherapy was associated with longer median response duration and survival than previous chemotherapy. Addition of Herceptin to chemotherapy increased response rates, time to disease progression and survival duration. Benefit was greatest in patients with high-level HER2 overexpression. Herceptin was well tolerated, with mild to moderate infusion-related reactions, usually seen with the first infusion only, being the most common event. Most patients respond to conventional supportive treatment. Cardiotoxicity, the most serious adverse event observed, occurred mainly in patients exposed to anthracyclines and was generally manageable. Thus, Herceptin represents a significant development in the management of HER2-positive breast cancer.

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1: Oncology. 2001;61 Suppl 2:31-6.

Related Articles, Links

Full Text

Dose scheduling--Herceptin.

Leyland-Jones B.

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Preclinical and phase I/II studies of Herceptin demonstrated a dose-related, non-linear pharmacokinetic profile. The results of a dose-finding study supported a regimen comprising an initial intravenous (i.v.) dose of 4 mg/kg with subsequent weekly doses of 2 mg/kg. However, pharmacokinetic and safety data suggested that increased dose and reduced frequency of Herceptin administration are feasible. In addition, evidence shows that Herceptin plus paclitaxel has additive antitumor efficacy in vitro, and this regimen produces significant clinical benefits. These observations form the rationale for conducting a phase I/II trial of Herceptin (8 mg/kg initial dose, 6 mg/kg maintenance dose) plus paclitaxel, both given 3-weekly. Preliminary results are promising, with serum trough Herceptin concentrations being similar and AUC being greater than those observed with weekly Herceptin plus 3-weekly paclitaxel. Two further trials are proposed: 3-weekly Herceptin as first-line monotherapy of metastatic breast cancer; and 3-weekly Herceptin with the oral 5-fluorouracil derivative, Xeloda (capecitabine). Subcutaneous (s.c.) administration of Herceptin would further simplify administration and studies are also underway to clinically evaluate s.c. administration of Herceptin in combination with paclitaxel. With the recent development of oral taxanes, it is predicted that combinations including an oral taxane, Xeloda and either 3-weekly or possibly s.c. Herceptin may become future therapies for breast cancer patients. Copyright 2001 S. Karger AG, Basel

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